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Neurophysiological correlates of sleep leg movements in acute spinal cord injury

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HIGHLIGHTS

- Leg movements during sleep are recorded in spinal cord injury patients with completely absent volitional activity in their lower limbs but they show clear periodicity only in a small subgroup of them.
- The disconnection from higher nervous structures, in these patients might allow the appearance of leg movements due to the activity of spinal generators not inhibited by higher influences.
- Leg movements during sleep in spinal cord injury patients might assume the periodic character when a genetic predisposition is present.

ABSTRACT

Objective: The objective of this study was to analyze the periodicity of leg movement activity emerging during sleep in a group of patients with spinal cord injury and to evaluate their pathophysiological features.
Methods: Twenty patients (16 males, mean age 34.0 years) with traumatic spinal cord lesions were recruited (5 cervical, 15 thoracic; 16 level A and 4 level B at the American Spinal Injury Association impairment scale). Periodicity of sleep leg movements was analyzed; electroencephalographic spectral analysis and heart rate were evaluated for 20 s preceding and 30 s following the onset of leg movements.
Results: Periodic leg movements during sleep (PLMS) index >5/h was found in only 4 patients and only 2 of these had PLMS index >15/h. Eleven patients (group I) did not show any increase in heart rate related to the occurrence of leg movements while the remaining 9 did (group II). Two patients in each group had American Spinal Injury Association impairment level B; 5 patients of group I and none of group II had cervical lesions while 6 patients of group I and all 9 of group II had thoracic lesions. Only 2 patients in group I presented clearly periodic leg movements during sleep and PLMS index >15/h. Electroencephalographic delta, alpha and beta bands around leg movements increased clearly in group II while the changes in group I were very limited or absent.
Conclusion: Leg movements during sleep are recorded in spinal cord injury patients with completely absent volitional activity in their lower limb but they show clear periodicity only in a small subgroup of them.
Significance: The disconnection from higher nervous structures, in patients with spinal cord injury might favor the appearance of leg movements due to the activity of spinal generators not inhibited by higher influences; correlated autonomic and electroencephalographic changes can be absent. This motor activity might assume the periodic character when a genetic predisposition is present.

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1. Introduction

Periodic leg movements during sleep (PLMS) and restless legs syndrome (RLS) have been reported to occur in myelopathy (Brown et al., 2000; de Mello et al., 1999; Lee et al., 1996; Nogues et al., 2000; Telles et al., 2011; Yokota et al., 1991) and a recent case report with spinal cord injury has shown that they might bear a striking resemblance with PLMS occurring in patients with RLS and respond to dopaminergic agents (Salminen et al., 2013). The same authors have reported that these PLMS are disconnected from cortical arousals and are not accompanied by changes in autonomic function, as indicated by the absent heart rate (HR) changes.

However, the pathophysiological basis of leg movements (LMs) occurring in spinal cord injury is incompletely known. The aims of this study were to analyze in detail the leg movement activity emerging during sleep in a group of patients with spinal cord injury in order to detect PLMS and to evaluate their pathophysiological features by analyzing their association with the autonomic function (HR) and brain rhythms. In particular, we also aimed at evaluating if the disconnection between LMs and autonomic changes is a phenomenon detectable in all patients with spinal cord injury or if it occurs only in a subgroup of them; in such a case, our aim was to detect eventual differences between these two subgroups.

2. Subjects and methods

2.1. Subjects

Twenty patients with traumatic spinal cord lesions (16 males and 4 females, mean age 34.0 years, 12.76 S.D.), referred to the spinal unit of the Niguarda Hospital (Milan, Italy) from September 2010 to December 2011, were recruited for this prospective observational study. Exclusion criteria were: (a) inability to give informed consent, (b) any significant head injury, (c) presence of tracheostomy at enrolment, (d) ventilator-dependent at enrolment, (e) other respiratory problems (chest infection, pneumothorax, haemothorax, effusion, intercostal catheter, sleep apnea). The location of the lesion and its extent was assessed in each patient by MRI, evoked potentials and electromyography. Five patients had lesions localized in the cervical region of the cord while the remaining 15 had lesions localized in the thoracic segment. The sensory and motor impairments presented by the patients were evaluated following the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Burns et al., 2012) of the American Spinal Injury Association (ASIA) and the ASIA impairment scale was assessed; at this scale, 16 patients presented the level A and the remaining four the level B. Prior to administering the ISNCSCI, it was established that all subjects had the cognitive ability to accurately respond to the test instructions. The polysomnographic data used for this study were collected after an average of 0.25 years (0.21 S.D.) from the traumatic event.

This study was approved by the local ethics committee and all subjects provided informed consent, according to the Declaration of Helsinki, before entering the study.

2.2. Polygraphic sleep recording

Each subject underwent a polysomnographic full night recording. Standard overnight polysomnography was performed in the ward in an attended setting using a portable sleep monitoring (AURA® PSG Ambulatory System; GRASS Technologies), including electro-encephalography, bilateral electro-oculography, chin and tibial electromyography, electro-cardiography, oronasal airflow, chest and abdominal effort (recorded using respiratory inductance plethysmography), pulse oximetry, and body position; patients with an apnea/hypopnea index $\geqslant 5$ were not included.

Sleep signals were sampled at 256 Hz and stored on hard disk for further analysis. EMG signals, in particular, were digitally band-pass filtered at 10–100 Hz, with a notch filter at 50 Hz.

At the beginning of each session and before the start of recording, the sleep technician checked that the amplitude of the EMG signal from the two tibialis anterior muscles was below 2 μV at rest.

2.3. Sleep scoring and detection of leg movements

Sleep stages were visually scored following standard criteria on 30-s epochs (Rechtschaffen and Kales, 1968); arousals were also detected following standard criteria (Iber et al., 2007). LMs during sleep were first detected by the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy), which allows their computer-assisted detection. With this software, the detection is performed by means of a human-supervised automatic approach controlled by the scorer, but for this study one scorer (R.F.) visually edited the detections proposed by the automatic analysis, before the computation of the various parameters which were automatically generated by the same software adopting the criteria set by the International RLS Study Group and endorsed by the World Association of Sleep Medicine (Zucconi et al., 2006). In particular, the PLMS index was calculated as the number of LMs included in a series of four of more, separated by more than five and less than 90 s, per hour of sleep.

We also obtained a distribution histogram of all inter-LM intervals and, subsequently, the number of intervals included in sequences of at least three, all 10–90 s long, was divided by the total number of intervals and we will refer to this ratio as the periodicity index (PI); this index can vary between 0 (absence of periodicity, with none of the intervals having a length between 10 and 90 s) to 1 (complete periodicity, with all intervals having a length between 10 and 90 s) (Ferri et al., 2006). PI is independent on the absolute number of LMs recorded and was calculated for all the subjects included in this study.

2.4. Heart rate and spectral EEG analysis

In this study, we analyzed HR and EEG spectral content accompanying LMs without arousals (Iber et al., 2007) and arousals without LMs. These LMs and arousals were included if they were not preceded or followed by another LM or arousal by at least 30 s. This time was chosen in order to avoid possible summation of the effects of separate movements on the variables under consideration; moreover, 30 s is well in the main peak of the inter-movement interval histogram expected for PLMS (Ferri et al., 2006). Up to five (but not less than 3) LMs and arousals were chosen from NREM sleep, for each patient.

In order to reduce or eliminate baseline variability of the parameters considered in this study and induced by intersubject and sleep stage differences, a fixed-time window of 50 s (20 preceding and 30 following the onset of each LM or arousal) was used, with its first 10 s which served for the calculation of the baseline; subsequently, each value was expressed as a percentage of this baseline value, for all parameters calculated around each LM or arousal. After this, individual averages were obtained for each individual included in the study, which served for the subsequent computation of the group average.

HR was measured and its value calculated for each round second by means of a linear interpolation between the measured values; EEG power spectra were calculated, after Welch windowing, by means of the Fast Fourier Transform. The power spectrum

was calculated for frequencies between 0.5 and 25 Hz from the C3-A2 or C4-A1 derivation, by means of a two-second-long sliding window which was moved along the 50-s epoch with steps of 1 s. Subsequently, the power spectrum for the following frequency bands was obtained for each time step (Delta = 0.5–4.0 Hz; Theta = 4.5–7.5 Hz; Alpha = 8.0–11.0 Hz, and Beta = 15.5–25.0 Hz). In this way, we obtained normalized synchronous graph of HR and of the different EEG bands which also allowed us to characterize the time relationships between them.

The method utilized for this analysis largely overlaps with the method previously reported in details by one of the authors of this paper (R.F.) (Ferri et al., 2007).

2.5. Statistical data analysis

For the statistical analysis, all comparisons were performed by means of the nonparametric Mann–Whitney test for unpaired datasets. However, because of the relatively limited number of subjects available and to rule out possible type II errors, we also calculated effect sizes using the Cohen's *d* value. The Fisher exact test was used for the comparison of frequencies.

The data analysis software system STATISTICA (StatSoft, Inc. 2004, version 6. www.statsoft.com) was used for statistical analysis.

3. Results

Between September 2010 and December 2011, 65 patients were admitted at the Spinal Unit of the Niguarda Hospital (Milan, Italy) for an acute spinal cord injury. Twenty patients met the selection criteria for this study.

Table 1 shows the sleep scoring parameters obtained in these patients. Even if no control group could be established for this study because recordings were carried out in the ward in an attended setting using a portable sleep monitoring (a condition that could not be replicated for normal controls); it is possible to note that only mild-to-moderate sleep architecture changes can be seen, characterized by the presence of a high number of arousals, sleep stage shifts and number of stage shifts. The details of sleep leg movement activity parameters are reported in Table 2. The average PLMS index found in the whole group of patients was around 11–12/h; however, PLMS index >5/h was found in only 4 patients and only 2 of these had PLMS index >15/h. No difference was evident between PLMS index during REM and NREM sleep.

All patients included in this study presented a clear HR increase accompanying the occurrence of arousals without LMs (Fig. 1, top panel). We defined an HR increase when there was at least one value above 105% with respect to the baseline (see Methods) in the time window between −5 s and +10 s relative to the onset of the events considered here (arousals without LMs and LMs without arousals). However, 11 out of the 20 patients did not show an increase in HR related to the occurrence of LMs while the remaining nine did (Fig. 1, bottom panel). On this basis, patients were subdivided into two subgroups: group I included the 11 patients without HR changes accompanying LMs and group II was formed by the remaining patients with a clear-cut HR increase accompanying LMs.

Two patients out of each group had a level B at the ASIA impairment scale while the remaining had all level A (not significant at the Fisher exact test). Five patients of group I and none of group II had lesions localized in the cervical region of the cord while six patients of group I and all nine of group II had lesions localized in the thoracic segment ($p < 0.03$ at the Fisher exact test). The time elapsed from the lesion to our evaluation was similar in the two groups (mean 0.26 ± 0.235 S.D. in Group I vs. mean 0.23 ± 0.196 S.D. in Group II, not significant at the Mann–Whitney test).

Group I patients tended to sleep worse than those of group II with a significantly higher amount of sleep stage 1 and a tendency to sleep less (total sleep time), to show more numerous stage shifts and a smaller percentage of REM sleep (Table 1). None of the LMs parameters showed a statistically significant difference between the two groups (Table 2); there was a tendency of Group I to show higher values especially regarding PLMS but with a smaller number of bilateral movements (large effect size).

The top panel of Fig. 2 shows the average intermovement interval distribution histogram obtained from the two groups of patients. In this graph a clear peak is evident in the interval range expected for PLMS (Ferri et al., 2006, 2008) in group I which is not detectable in group II; however, no significant statistical difference was found between the graphs. This lack of significance is explained by the analysis of the individual intermovement interval distribution histograms obtained from all patients included in this study, reported in the bottom panel of Fig. 2. This analysis shows that the peak observed in the average histogram was due to the presence of a similar peak in only two patients belonging to group I (both with PLMS index >15/h) and in none of group II. The inset on the right top corner of the same panel shows the individual values of PI obtained in each patient.

Finally, Fig. 3 shows the changes in HR and power of the different EEG bands accompanying leg movements during NREM sleep in the two subgroups of patients. Clear increases were evident for the delta, alpha and beta band in patients of group II while the changes in EEG spectral content accompanying LMs in group I were very limited or absent.

4. Discussion

Despite the fact that PLMS in patients with spinal cord injury have been reported by several studies in the past (Brown et al., 2000; Lee et al., 1996; Nogues et al., 2000; Salminen et al., 2013),

Table 1
Comparison between the sleep architecture parameters found in the two subgroups of patients.

	All patients ($n = 20$)		Group I ($n = 11$)		Group II ($n = 9$)		Mann–Whitney	Effect size
	Mean	S.D.	Mean	S.D.	Mean	S.D.	$p<$	Cohen's *d*
Time in bed, min	595.4	81.95	571.8	72.10	624.2	88.04	NS	−0.652
Sleep period time, min	561.9	83.92	549.6	71.72	577.0	99.14	NS	−0.317
Total sleep time, min	480.4	88.72	457.5	65.84	508.4	108.02	NS	−0.570
REM latency, min	139.5	79.69	124.0	64.71	158.4	95.48	NS	−0.422
Stage shifts/hour	18.1	5.01	19.3	4.57	16.6	5.38	NS	0.548
Awakenings/hour	7.7	4.09	7.8	4.38	7.5	3.97	NS	0.081
WASO,%	14.5	7.96	16.4	8.33	12.2	7.26	NS	0.538
S1,%	8.9	4.05	10.5	4.08	6.8	3.16	0.007	0.999
S2,%	41.2	13.12	38.9	12.96	44.0	13.54	NS	−0.380
SWS,%	22.1	8.69	22.9	10.32	21.2	6.65	NS	0.198
REM,%	13.3	6.82	11.2	7.24	15.8	5.66	NS	−0.699

Table 2
Comparison between the sleep leg movement activity parameters found in the two subgroups of patients.

	All (n = 20)		Group I (n = 11)		Group II (n = 9)		Mann–Whitney	Effect size
	Mean	S.D.	Mean	S.D.	Mean	S.D.	$p<$	Cohen's d
Total sleep								
Total LM index, number/hour	15.4	31.30	22.8	41.34	6.4	4.90	NS	0.556
PLMS index, number/hour	11.5	30.87	19.1	40.74	2.1	2.77	NS	0.591
Isolated LM index, number/hour	4.0	2.93	3.7	3.23	4.4	2.65	NS	−0.231
NREM sleep								
Total LM index, number/hour	15.1	30.49	22.1	40.26	6.5	5.51	NS	0.545
PLMS index, number/hour	11.1	29.73	18.5	39.20	2.0	3.26	NS	0.593
Isolated LM index, number/hour	4.0	3.01	3.6	3.25	4.4	2.79	NS	−0.277
REM sleep								
Total LM index, number/hour	15.8	34.10	23.8	45.08	6.0	5.20	NS	0.554
PLMS index, number/hour	11.8	34.42	20.2	45.55	1.6	2.53	NS	0.578
Isolated LM index, number/hour	3.9	4.51	3.5	4.75	4.4	4.43	NS	−0.186
Bilateral LM,%	14.4	12.78	9.5	10.57	19.9	13.45	NS	−0.854
Number of PLMS sequences	2.8	3.88	2.9	4.32	2.6	3.50	NS	0.090
PLMS sequence duration, s	56.9	160.49	93.2	212.63	12.5	24.95	NS	0.533
PLMS duration NREM, s	1.5	1.05	0.5	0.79	1.4	1.68	NS	−0.730
PLMS duration REM, s	0.9	1.32	1.5	0.93	1.5	1.23	NS	0.014
Isolated LM duration NREM, s	1.3	0.76	0.7	0.78	1.0	0.78	NS	−0.367
Isolated LM duration REM, s	0.9	0.77	1.1	0.80	1.5	0.69	NS	−0.521
Periodicity index, total	0.161	0.254	0.204	0.327	0.108	0.121	NS	0.390
Periodicity index, NREM	0.152	0.258	0.209	0.323	0.082	0.134	NS	0.514
Periodicity index, REM	0.115	0.271	0.170	0.360	0.053	0.107	NS	0.442
PLMS with arousal index, number/hour	0.9	1.28	1.0	1.49	0.8	1.06	NS	0.115

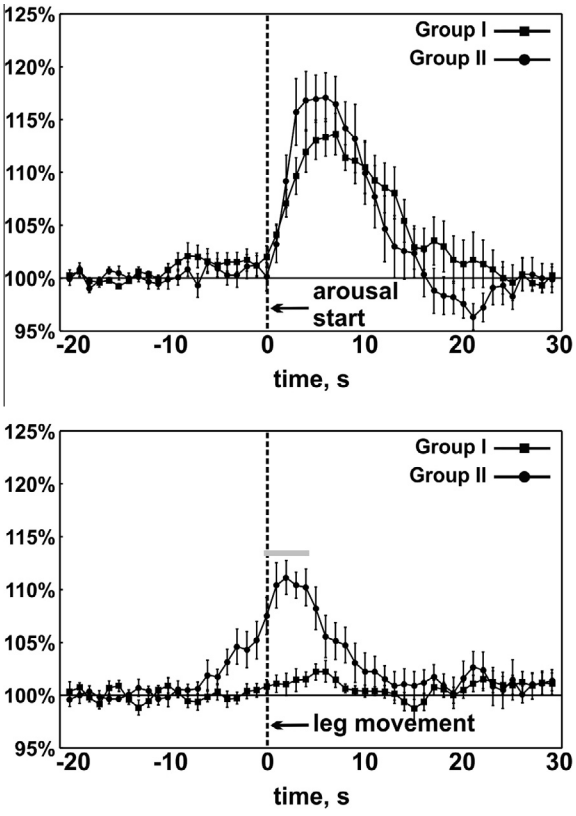

Fig. 1. Changes in HR accompanying arousals (top panel) and leg movements (bottom panel) during NREM sleep in the two subgroups of patients. Data are shown as a percentage of the average value calculated over the first 10 s of the window, from −20 to −10 s before the arousal or LM onset (dashed vertical line). Whiskers indicate SE. The horizontal grey band indicates a statistically significant difference at the Mann–Whitney test followed by the Bonferroni correction ($p < 0.05$).

our analysis shows that genuine PLMS with a clear periodicity are detectable only in a minority of these patients. The reasons of this reside essentially in the low number of patients reported in the majority of the studies cited above, which typically included single case reports or small case series. In only one report, 26 patients with syringomyelia or syringobulbia were recruited (Nogues et al., 2000). Additionally, the presence of PLMS has been almost exclusively assessed by means of the measurement of the PLMS index; only in one single case report the patient study (Salminen et al., 2013) included the same analysis used here, able to pick up periodicity. In fact, it is now clear that even randomly generated sequences of intervals can give rise to a high PLMS index (Ferri, 2012) if they are analyzed with the current standard rules (Iber et al., 2007; Zucconi et al., 2006). Thus, the PLMS index alone cannot be considered sufficient to assess periodicity of LMs during sleep (Ferri, 2012).

Nevertheless, we have found two patients with clearly periodic LMs but it is not possible to establish if these movements were present before the traumatic spinal cord injury or not; thus, with our data it is not possible to support the claim that PLMS can be more frequent after spinal cord injury. The results of the present study, together with several earlier reports in the literature (Birinyi et al., 2006; Trotti et al., 2008), agree with the data indicating that PLMS have a strong genetic background (Stefansson et al., 2007). It is thus possible, if not probable, that the two patients found to have PLMS in the current study with a time structure very similar to that of typical PLMS of RLS (Ferri et al., 2006) may be genetically predisposed for this motor phenomenon and, possibly at risk for RLS.

Given the above considerations, we have essentially studied the HR and spectral EEG changes associated with LMs rather than PLMS in this study. However, these changes are expected to be similar to those accompanying PLMS (Ferri et al., 2007). First of all, we should remark that in all patients clear changes in HR were observed in association with the occurrence of arousals during NREM sleep. This allowed us to exclude the presence of patients with absent arousal-related HR changes. Slightly less than half of the patients showed similar changes associated with the occurrence of PLMS (without arousals); the remaining patients did not show discernible HR changes.

Having in mind the recent single case report mentioned above (Salminen et al., 2013), we expected to find most, if not all, patients

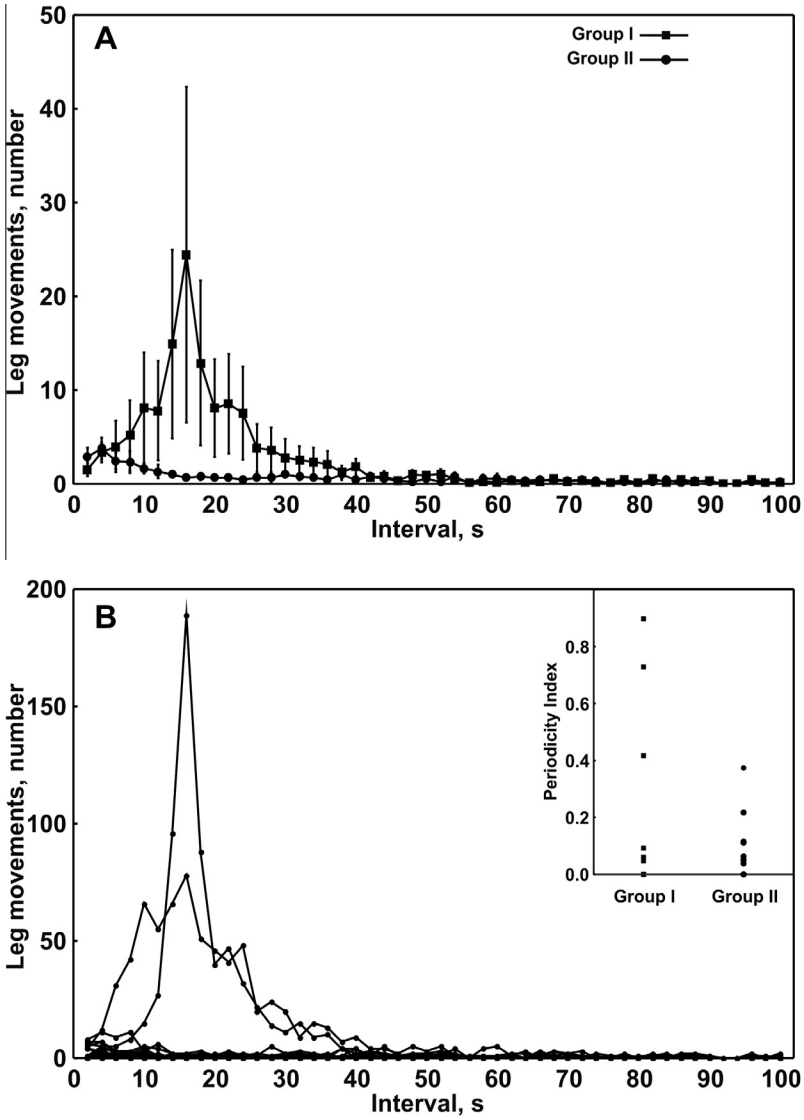

Fig. 2. A. Average intermovement interval distribution histogram obtained from the two subgroups of patients. Whiskers indicate SE. B. Individual intermovement interval distribution histograms obtained from all patients included in this study. The inset on the right top corner shows the individual values of periodicity index obtained in each patient.

with no LM-related HR and EEG changes because most of our cases had a level "A" at the ASIA impairment scale, indicating a complete spinal cord injury (no motor or sensory function below the neurological lesion). We might have expected to detect HR and EEG changes correlated to LMs only in the four patients with a level "B" at the ASIA impairment scale which indicates an incomplete spinal cord injury (sensory but not motor function preserved below the neurological lesion level). Unexpectedly, we found that not only two patients with a level "B" at the ASIA impairment scale had clear HR and EEG changes associated to LMs but also seven patients with a level "A". It is not easy to explain this finding and the most obvious interpretation might be that some surviving small spinal connections might exist in these patients that are not detectable at MRI and that are not picked up by the neurological examination too. Another nontrivial possibility is that other movement involving the upper limbs or other muscle district, synchronized with leg movements, might be present in these patients that are responsible for the HR and EEG changes observed. It is commonly known that PLMS are not restricted to legs but are often part of a more complex sleep motor pattern, as reported earlier (Provini et al., 2001). Finally, it is possible to believe that some extra-spinal autonomic nervous system connections might underlie these findings.

Our results found in the two patients with genuine PLMS are very similar to the findings by Salminen et al. (2013) in their single case report. Additionally, also brain rhythms analyzed by means of EEG spectral analysis showed increases in the delta, alpha and beta bands associated to LMs only in patients with HR increase (group II) and absent in the others. The changes observed in brain rhythms resemble strictly those previously reported for PLMS and nonperiodic LMs in RLS (Ferri et al., 2007). All this confirms once more that LMs during sleep can be dissociated from arousals (and its autonomic correlates) in a variety of conditions including pharmacological interventions (Manconi et al., 2012), experimental procedures (Ferri et al., 2013), and pathological states inducing an anatomical/functional disconnection between the spinal cord and higher nervous structures (Salminen et al., 2013).

The possibility to dissociate events that occur often as a cluster, such as cortical arousals, autonomic events, and PLMS, suggests that the inter-relationships between these events are not likely to follow the simple paradigm of any one event leading to another (Ferri, 2006), this can be inferred not only from the current study

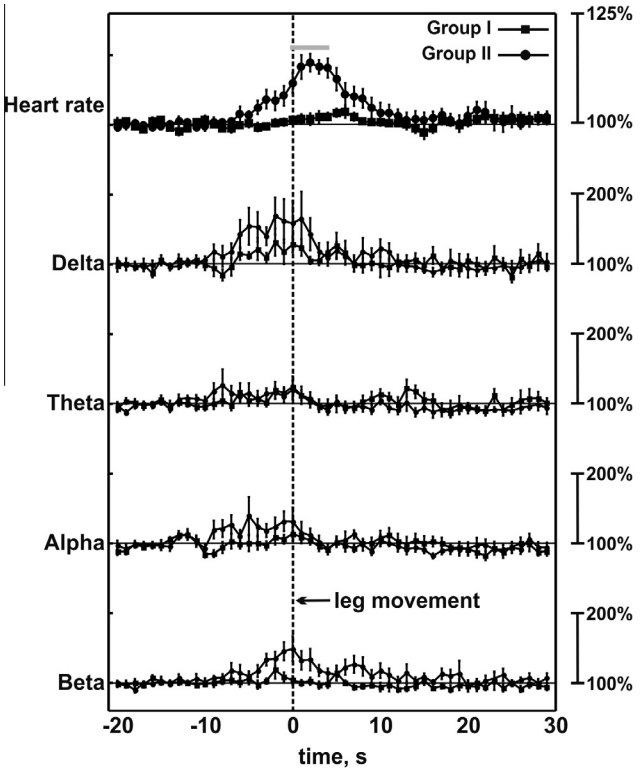

Fig. 3. Changes in HR and power of the different EEG bands accompanying leg movements during NREM sleep in the two subgroups of patients. Data are shown as a percentage of the average value calculated over the first 10 s of the window, from −20 to −10 s before the LM onset (dashed vertical line). Whiskers indicate SE. The horizontal grey band indicates a statistically significant difference at the Mann–Whitney test followed by the Bonferroni correction ($p < 0.05$).

but also from previous work (Ferri et al., 2010; Ferri and Zucconi, 2008; Manconi et al., 2011, 2012; Pennestri et al., 2007). On a more speculative level, the lack of a cause/effect relationship between these events does not exclude the possibility that, when they do occur concurrently, one modifies the biological effects of the other (Yang et al., 2006). The resulting possibly enhanced effect may represent the basis of adverse consequences of various clinical conditions in which PLMS are particularly abundant such as RLS (Walters and Rye, 2010; Winkelman et al., 2008) or periodic limb movement disorder (Saletu et al., 2001).

Thus, our results show that LMs during sleep are recorded indeed in patients with completely absent volitional activity in their lower limb but they show clear periodicity only in a small subgroup. The small number of patients with genuine PLMS does not allow us to infer more detailed considerations regarding the level of the lesion (cervical in one and thoracic in the other) or the level of clinical impairment (ASIA impairment index A in one and B in the other); however, our data seem to agree with the idea that the disconnection from higher nervous structures, in these patients might allow the appearance of LMs due to the activity of spinal generators not inhibited by higher influences. This motor activity might assume the periodic character when a genetic predisposition (Stefansson et al., 2007) is present.

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